URINARY INCONTINENCE

We now know more about incidence, the fascial sling versus Burch colposuspension, complication rates of mid-urethral slings, and Botox for detrusor overactivity

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The past year has seen the publication of much useful evidence regarding urinary incontinence, from both epidemiologic studies and clinical trials. Research into the pathophysiology of incontinence continues to move forward, slowly but surely, measured not in breakthroughs but in gradually increasing knowledge of how the urethra and bladder function in the continent person and how that function can break down, leading to incontinence and other urinary symptoms.

Highlighted here are four notable studies from 2007, as well as progress notes on a trial mentioned early this year in Examining the Evidence (January issue).

New data clarify incidence and uncloak the effect of weight gain

Townsend MK, Danforth KN, Liffort KL, et al. Incidence and remission of urinary incontinence in middle-aged women. Am J Obstet Gynecol. 2007;197:167.e1–167.e5.

Townsend MK, Danforth KN, Liffort KL, et al. Body mass index, weight gain, and incident urinary incontinence in middle-aged women. Obstet Gynecol. 2007;110:346–353.

Studies of urinary incontinence in numerous populations have reported its prevalence—i.e., the percentage of people who have the condition at any point in time—but few have attempted to define its incidence—i.e., the rate at which it develops during a defined period.

Incidence is a true rate, described with a unit of time in the denominator. Prevalence is not a rate (although it is commonly referred to as such) and is described as a percentage only, without time in the denominator. With that distinction in mind, it is easy to see why prevalence data greatly outnumber incidence data: Prevalence can be obtained by means of cross-sectional study, with one-time collection of data. In contrast, incidence data require a population that is free of the condition of interest at baseline; that population is then followed to determine how many people who were initially free of the condition go on to develop it.

Lack of a standard definition makes it hard to measure incontinence

Reported prevalence can range from less than 10% to more than 90%, depending on how incontinence is defined:

IN THIS ARTICLE

- **Very low prevalence** is found when the definition is limited to persons with the greatest severity or frequency of symptoms
- at the other end of the spectrum, **very high prevalence**—even approaching 100%—can be found using a definition that includes people who have "ever" leaked urine.

The same issues complicate estimates of incidence. Because there is no consensus over what constitutes a clinically significant threshold for incontinence, investigators are forced to develop their own definitions.

In a pair of studies, Townsend and colleagues neatly circumvent this problem. Using data from the Nurses' Health Study II, they used a series of definitions of incontinence, ranging from less severe to more severe, to describe their findings in ways that are easily transferred to clinical practice. They focused their attention on women aged 36 to 55 years to estimate the incidence of incontinence over a 2-year period. At baseline, women were considered at risk of incident incontinence if they reported never leaking or leaking only a few drops less than once a month. Three categories of incontinence were then defined, based on symptoms 2 years later:

- **incident incontinence:** any urine loss, defined as leaking 1–3 times a month
- **frequent incontinence:** urine loss at least once a week
- **severe incontinence:** urine loss at least once a week of sufficient volume to at least wet underwear.

Incidence rose with BMI, weight gain

In almost 34,000 continent women from 2001 to follow-up in 2003, the overall (average) incidence of urinary incontinence was 6.9 women for every 100 woman-years. Frequent incontinence developed in, on average, 1.8 women for every 100 woman-years; severe incontinence, in 0.6 women for every 100 woman-years.

Using multivariable logistic regression models, the authors analyzed the likelihood of incident incontinence by body mass index (BMI) and estimated weight gain from the age of 18 until 2001. For either variable, odds ratios (OR) showed a highly significant trend ($P<.001$) for an increased risk of incident incontinence.

For example, at a BMI greater than 35 kg/m^2, the likelihood of:

- any incontinence increased by a factor of about 2 (OR, 2.11; 95% confidence interval [CI], 1.84–2.42)
- frequent incontinence increased by a factor of almost 4 (OR, 3.85; 95% CI, 3.05–4.85)
- severe incontinence increased by a factor of more than 5 (OR, 5.52; 95% CI, 3.72–8.18).

The trend for weight gain was similar, with a gain of more than 30 kg showing odds ratios and 95% confidence intervals of similar magnitude to those seen with a BMI greater than 35.

But one third of incontinent women improved after 2 years

Although urinary incontinence is usually understood as a chronic condition, albeit under the influence of other factors, such as weight gain, data on remission are even scarcer than data on incidence. Using the same dataset, the authors determined that almost 31,000 women were incontinent at baseline in 2001, with incontinence occurring at least monthly. Complete remission, defined as no leaking in 2003, occurred in almost 14% of women. One third reported improvement, defined as either complete remission or a decrease in leaking frequency from 2001 to 2003.

It's interesting that complete remission was more common in younger women. It also was more common in women who experienced frequent incontinence than in those who reported occasional incontinence. The remaining percentage of women—almost 60%—reported a similar or increased frequency of incontinence over the 2 years of follow-up.

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At a BMI greater than 35, severe incontinence increased by a factor of 5

The authors did not collect data on treatment. Estimates of persistence, improvement, and remission could be affected, therefore, if women received effective treatment between 2001 and 2003. However, only about one third of women reported mentioning their symptoms to a physician, and only 13% reported receiving treatment for incontinence. The magnitude of the effect of treatment on remission or improvement of urinary incontinence symptoms therefore seems limited.

Women remain reticent about incontinence

Several points underline the clinical importance of these data, including the relatively high incidence of incontinence symptoms and the strong influence of BMI and weight gain on that incidence. Also notable, and described in previous studies, is the vast underreporting and undertreatment of incontinence in women—an observation that should motivate all clinicians to include screening for urinary incontinence as part of regular well-woman care. Clinicians should also be prepared to refer women with incontinence or to initiate evaluation and management.

Some reports have suggested that the stigma of urinary incontinence has diminished slightly in light of widespread direct-to-consumer advertising for products related to the care (e.g., pads) or treatment (e.g., pharmaceuticals) of incontinence. The data from Townsend and colleagues are relatively recent, yet the majority of women failed to report their symptoms, and an even higher percentage received no treatment. The authors recommend that health-care providers initiate a discussion of urinary symptoms even in middle-aged women, who may be targeted for screening less frequently than older women.

In fascial sling vs Burch, sling prevails but is linked to more adverse effects

Albo ME, Richter HE, Brubaker L, et al, for the Urinary Incontinence Treatment Network. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007;356:2143–2155; comment: 2198–2200.

Eagerly anticipated results of the Urinary Incontinence Treatment Network's first surgical trial, which compared the fascial sling procedure with Burch colposuspension for stress incontinence, were published in May in the *New England Journal of Medicine*. The Urinary Incontinence Treatment Network is a multicenter clinical trials group that was established in 2000 and is sponsored by the National Institutes of Health (specifically, by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Child Health and Human Development).

Women were eligible for the trial if they experienced symptoms of stress incontinence; symptoms of mixed incontinence were allowed as long as stress symptoms predominated. Of 655 women in the trial, 326 were randomly assigned to undergo placement of an autologous rectus fascia pubovaginal sling, and 329 were randomized to Burch colposuspension.

Overall success was defined as:

- negative pad test
- no urinary incontinence reported in a 3-day diary
- negative stress test to cough and Valsalva maneuver

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Overall success and "stress success" were slightly higher in women who underwent sling placement than in those treated by Burch

- no self-reported symptoms of stress incontinence
- no retreatment for stress incontinence.

"Stress success," or stress continence, was defined using the last three criteria.

At 2 years after the index surgery, 520 women (79%) were available for follow-up. Overall success and stress success were slightly higher in women who underwent sling placement than in those treated by Burch: overall success, 47% versus 38%, and stress success, 66% versus 49%, respectively. However, women who had slings experienced more adverse outcomes, including urinary tract infection, difficulty voiding, and postoperative urge incontinence.

Success rates were much lower than previously reported

These findings are particularly striking because the success rates are lower than in previous reports—and lower than the figures commonly used by surgeons to counsel women about likely results. "Success" for either procedure has been commonly quoted in the 80% to 90% range, not the 30% to 40% range found here. The authors are to be commended for the stringent definition of "success," which included elements that invariably result in a lower success rate. It is these numbers that women are most interested in when they are considering this type of surgery.

The difference between sling and Burch procedures was particularly remarkable in regard to stress success (17 percentage points). The smaller difference seen for overall success (9 percentage points) can be attributed to the increase in postoperative urge incontinence among women undergoing the sling procedure.

If the other adverse events associated with the sling procedure (i.e., urinary tract infection and voiding difficulty) had been included in the composite measure of success, it seems possible, if not likely, that a smaller difference—or no difference at all—would have been seen between the sling and Burch groups.

Additional data still to come

Follow-up of women in this trial has been extended for up to 5 years and should provide much-needed information on longer-term results after these surgeries.

Transobturator mid-urethral sling linked to fewer complications

Sung VW, Schleinitz MD, Rardin CR, Ward RM, Myers DL. Comparison of retropubic versus transobturator approach to midurethral slings: a systematic review and meta-analysis. Am J Obstet Gynecol. 2007;197:3–11.

In this Update 1 year ago, I remarked on the need for more comparative information about the various mid-urethral slings currently on the market, particularly in regard to complications—information necessary to make recommendations and guide clinical decision-making.

Originally, the procedure for mid-urethral sling placement was modified from the retropubic approach to the obturator approach with the aim of reducing the risk of major bladder and urethral injury and vascular complications (**FIGURE 1**, page 44). Recent data suggest that that goal has been achieved. In a systematic review and meta-analysis of 17 studies that compared retropubic and transobturator approaches, Sung and colleagues found the transobturator route to be associated with fewer complications.

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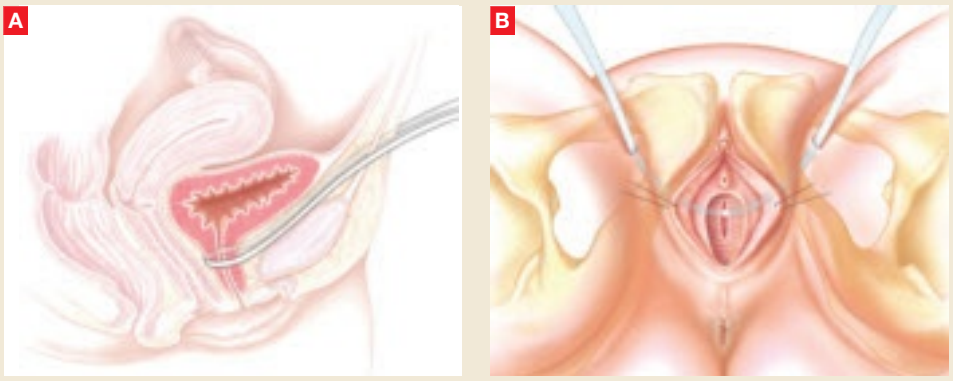
Data suggest that the transobturator mid-urethral sling reduces the risk of major bladder and urethral injury and vascular complications

FIGURE 1

Transobturator approach lives up to promise



The retropubic approach (**A**) was modified to create the transobturator approach (**B**), with the aim of protecting the bladder, urethra, and vascular structures. A recent meta-analysis indicates that this goal was achieved.

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The pooled odds ratio for complications from transobturator sling placement was 0.40, compared with the retropubic approach

Subjective and objective outcomes were similar for the two approaches

Overall, 492 women in six trials were randomly assigned to receive either a retropubic or transobturator mid-urethral sling for treatment of stress incontinence. Although some trials specified exactly which device was used, others did not. Follow-up ranged from 1 to 15 months.

Because the studies used different definitions of objective success as outcomes, it was not possible to obtain a pooled estimate for objective outcomes. However, the authors were able to calculate a pooled estimate for *subjective* outcomes by defining subjective success as a woman reporting either continence or improved status after surgery, and by defining failure as a woman reporting unchanged or deteriorating incontinence status.

The pooled odds ratio for subjective failure after transobturator placement of a mid-urethral sling was 0.85, compared with the retropubic approach (95% CI, 0.38–1.92). Results were relatively stable despite changes in definitions of success and failure and restriction to studies with more than 1 year of follow-up. Sung and colleagues concluded that evidence was insufficient to support one or the other approach in regard to subjective or objective outcomes.

Bladder perforation was most common complication

Findings regarding complications were more conclusive. Again drawing on data from six randomized trials, the authors estimated a pooled odds ratio for complications from transobturator placement of 0.40, compared with the retropubic approach (95% CI, 0.19–0.83). Using data from both randomized trials and cohort studies, the most common complications were:

- **bladder perforation:** 3.5% for retropubic placement, 0.2% for the transobturator route
- **hematoma:** 1.5% for retropubic placement, 0.08% for the transobturator route.

More definitive data are in the works

As noted here last year, the Urinary Incontinence Treatment Network is enrolling women with stress or stress-predominant mixed incontinence in a randomized trial to compare the retropubic and transobturator approaches for mid-urethral slings. With a sample size of 655 women and 2-year follow-up planned, this trial should be adequately powered to detect clinically important differences, if they exist, in both continence outcomes and complications. Enrollment is projected to close in 2008, with results to follow 2 years later.

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Botox injection for detrusor overactivity is no quick fix after all

Interest continues to rise in treating detrusor overactivity—with or without incontinence—with botulinum toxin A. Only one commercial product is available in the United States, sold by Allergan under the trade name Botox. Last year, the Pelvic Floor Disorders Network, sponsored by the National Institute of Child Health and Human Development and the Office of Research in Women's Health, began a placebo-controlled trial of cystoscopic detrusor injection of 200 U of Botox versus placebo, randomized in a 2:1 ratio, for women with incontinence caused by refractory idiopathic detrusor overactivity (**FIGURE 2**, page 48).

Although a sample size of 210 subjects was planned, enrollment was halted after 43 women received injections (28 with Botox, 15 with placebo). The reason: A higher-than-expected rate of urinary retention.

The trial had defined urinary retention as:

- use of catheterization for more than 4 weeks after the date of injection, or
- postvoid residual (PVR) urine of 200 mL or more at the 4-week visit. (The protocol mandated that a patient with this degree of retention be catheterized or that catheterization be considered by the clinician.)

Rate of urinary retention proved to be much higher than anticipated

At the time the study protocol was finalized, most existing studies had focused on patients with neurogenic detrusor overactivity incontinence, many of whom already had impaired bladder emptying treated with self-catheterization. Communication with clinicians using Botox off-label for idiopathic detrusor overactivity incontinence suggested that the occurrence of urinary retention requiring intervention was less than 5%. However, of the 28 women who received Botox, 12 experienced urinary retention; most of these women (9 of 12) had elevated PVR at 4 weeks after injection. Although this elevation was temporary, some women required catheterization for months.

Of the 43 women included in the trial, 12 (28%) experienced urinary retention. However, counting only subjects who received Botox, the proportion with retention was 12 of 28 (43%). None of the women who received placebo experienced urinary retention.

There was also a higher incidence of urinary tract infection in women who developed retention after Botox injection and performed self-catheterization.

Follow-up continues for all 43 subjects, as the protocol provided for monitoring up to 1 year after injection. A full report on the safety and effectiveness of Botox for idiopathic detrusor overactivity in this trial is pending (manuscript submitted for publication).

Catheterization may raise risk of infection without providing a benefit

Ideal management of women who experience elevated PVR after Botox injection is unclear. Many clinicians wonder whether treatment—i.e., catheterization—is necessary for the type of impaired bladder emptying that occurs after Botox injection. It is even possible that catheterization increases the risk of urinary tract infection (or colonization) without providing a benefit to balance that risk.

Botox may still be an option, provided the patient is counseled about risks

Our understanding, albeit incomplete, of the mechanism of action when Botox is used to treat detrusor overactivity does not suggest an increased risk of elevated intravesical pressure leading to ureteral reflux and kidney damage; in fact, normal

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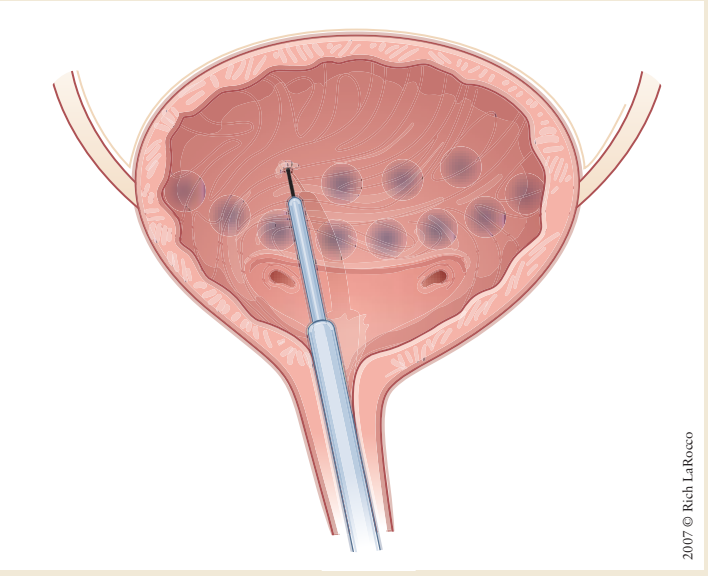
Because of a higher-than-expected rate of urinary retention, enrollment was halted after 43 women received Botox injections

FIGURE 2

Botox relieves detrusor overactivity—but only temporarily



A trial intended to encompass 210 women was halted early because the rate of urinary retention was significantly higher than expected. Twenty-eight women underwent injection of 200 U of Botox, and almost half were classified as having urinary retention 4 weeks after the procedure.

bladder pressure has been observed in the few studies in which it was measured after Botox injection. However, until we have further information about the short- and long-term risks, if any, of elevated PVR after Botox injection, clinicians should counsel patients about this possibility before proceeding with off-label use of Botox for detrusor overactivity.

Patients unlikely to tolerate repeated Botox injection over several years

Whether or not Botox in its current form will prove to be a useful treatment for women who have detrusor overactivity incontinence remains to be proven conclusively. Even if Botox relieves symptoms, especially in women who have not obtained relief from other treatments, current evidence suggests that the effect is time-limited, probably on the order of several months—although occasional patients obtain relief of greater duration, suggesting an effect that lasts beyond direct Botox action.

Given that most women experience these symptoms on a chronic basis—perhaps especially those who are refractory to usual treatment—it seems unlikely that repeated injections at intervals of only several months can be sustained for years. Ideally, development of second-generation products and further research will produce longer-lasting effects without the need for repeated injections at regular intervals. ■

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